REMARKS

I. The Subject Matter of the Claims

In general, the subject matter of the claims relates to monoclonal antibodies specifically reactive with α_d integrin which also modulate TNFα activity. The foregoing amendment is in the revised amendment format as provided in 1267 OG 106. Accordingly, the provisions of 37 C.F.R. § 1.21, requiring submission of clean and marked-up versions of the replacement paragraphs and claims, are waived.

II. The Objections to the Specification

Applicants note the Examiner's objection regarding the formal drawings and will submit final drawings upon notification of allowance.

III. Amendments

Support for the amendment to claims 11 and 12 can be found throughout the specification. For example, page 41, lines 21-29, of the specification teaches that α_d/CD18 binds to ICAM-R, while page 43, lines 13-21, demonstrates that α_d binds VCAM-1. Further support for the amendment is set out in Section IV.A.

IV. Patentability Arguments

A. The Rejection of Claims 11, 12 and 14 under 35 U.S.C. §112, First Paragraph, May Properly be Withdrawn

The Examiner maintains the rejection of claims 11, 12 and 14 under 35 U.S.C. §112, first paragraph, as assertedly not being enabled by the specification for "any α_d specificity as the target of the claimed methods." The Examiner contends that the specification does not enable any α_d that hybridizes to the complement of the polynucleotide of claim 11(a) or (b). The Examiner alleges that Applicants have not provided sufficient functional characteristics of the α_d molecule set out in claims 11(c) and 12(c) to enable the claimed α_d specificity.

Applicants submit that amendment to claims 11 and 12 to recite that said α_d polypeptide retains a biological activity of an α_d polypeptide obviates this rejection. The

specification describes several functional characteristics of an α_d polypeptide, including, for instance, interaction of α_d with various binding partners.

For example, in Example 12, at page 41, lines 21-29, the specification discloses functional properties of α_d binding. The specification discloses that CD11a/CD18 binds ICAM-1, while α_d/CD18 does not bind ICAM-1, demonstrating that α_d exhibits unique properties compared to other β_2 integrin alpha subunits. The specification also teaches that α_d/CD18 binds to ICAM-R with 3-5 fold greater affinity than control protein (BSA). Page 42, lines 10-24, of the specification teaches that that α_d binds ICAM-R within a different domain than CD11a. The specification further discloses, at page 44, lines 7-8, that the α_d polypeptide does not bind to a mutant ICAM-R. Thus, α_d is readily identified based on its ability to bind ICAM-R, its affinity for binding ICAM-R, and the region of ICAM-R it binds compared to other ligands.

Moreover, at page 43, lines 13-21, the specification demonstrates that α_d binds VCAM-1, and compares the rate of α_d/VCAM-1 binding with VCAM-1 binding to control protein or E-selectin. The specification also indicates that α_d/VCAM-1 binding is partially blocked by an antibody to the first domain of VCAM-1, thereby functionally describing where in the VCAM-1 protein α_d may bind.

Additional examples describing α_d binding to its binding partners may be found at, for instance, page 43, lines 7-11; page 43, lines 21-24; and page 158, lines 20-30 which describe the binding of α_d to specific VCAM-1 domains. Thus, the specification discloses numerous functional properties of α_d that a worker of skill could use, without undue experimentation, to obtain an α_d molecule used in the methods of the invention.

Additional structural comparisons with related integrins (see page 31, lines 8-13) indicate that the cytoplasmic region of α_d differs markedly from that of CD11a, CD11b or CD11c, suggesting that an α_d polynucleotide or polypeptide would not share high homology with other CD11 molecules. Table 1, page 121, shows that other CD18 binding partners, CD11a, CD11b, and CD11c, which do not share many functional characteristics with α_d, demonstrate low amino acid homology with α_d. However, sequences with higher amino acid homology to α_d, e.g. orthologous α_d molecules from rat (Example 20, page 79), mouse (Examples 28 and 29, pages 105-113), and rabbit (Example 33, page 119) are shown to hybridize with the human α_d sequence set out in SEQ ID NO: 1, and also share nearly identical functional properties. These

molecules, and isolation of additional human α_d variants in Example 5, provide support for species within the genus of polynucleotides that hybridize to SEQ ID NO: 1.

Any α_d-encoding molecule identified to hybridize to the polynucleotide of SEQ ID NO: 1 or to a polynucleotide encoding the polypeptide of SEQ ID NO: 2, thus sharing structural properties of α_d, are then assessed for their functional properties, as described above (e.g., ICAM-R or VCAM-1 binding, lack of ICAM-1 binding, blockade of binding by specific antibodies), which identify a molecule as an α_d molecule. As such, Applicants submit that the rejection of claims 11, 12 and 14 under 35 U.S.C. §112, first paragraph, as lacking enablement, may properly be withdrawn.

B. The Rejection of Claims 11, 12 and 14 under 35 U.S.C. §102(b), May Properly be Withdrawn.

The Examiner maintains the rejection of claims 11, 12 and 14 under 35 U.S.C. §102(b) for assertedly being anticipated by Gallatin, which allegedly teaches methods of treating immune or inflammatory responses with antibodies to α_d. The Examiner asserts that inhibition of TNFα activity is an inherent property of the antibodies disclosed by Gallatin.

Applicants respectfully disagree. An inherent property has been defined wherein "an inherent property has to flow naturally from what is taught in a reference." *In re Oelrich,* 212 USPQ 323; *Stoller v Ford,* 18 USPQ 2D 1545. Although MPEP 2145.II states that "another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious" (*Ex parte Obiaya*, 227 USPQ 58), it follows that, if the advantage does not flow naturally from the suggestion in the prior art, it should not be deemed obvious.

Moreover, for a reference to anticipate, that single reference must disclose each and every limitation of the claimed invention. MPEP 2131.01 (III) states that to serve as anticipatory art when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill (*emphasis added*). For a reference that is silent about an asserted inherent characteristic, inherent anticipation requires

that the missing descriptive material is "necessarily present," not merely probably or possibly present, in the prior art. *In re Robertson* , 49 USPQ2d 1949, (citing *Continental Can Co. USA, Inc. v. Monsanto Co.*, 1268, 20 USPQ2d 1746 (Fed. Cir. 1991)).

The present invention involves methods for specifically inhibiting TNFα activity from macrophages or splenic phagocytes using monoclonal antibodies to integrin α_d. Gallatin neither discloses nor suggests any ability of α_d-specific antibodies to modulate TNFα activity. Gallatin simply describes a method for producing α_d-specific antibodies and discloses a general use for the disclosed antibodies, without giving <u>any</u> particular examples of α_d-specific monoclonal antibodies or methods for their use other than a generic use for treating immune or inflammatory responses. The Examiner's support that Gallatin provides disclosure of use of α_d-specific antibodies for treatment of immune and inflammatory responses is found at page 4, lines 20-26 of the specification, or in Gallatin at column 3, paragraph 2:

> "The significance of β_2 integrin binding activity in human immune and inflammatory responses underscores the necessity to develop a more complete understanding of this class of surface proteins. Identification of yet unknown members of this subfamily, as well as their counterreceptors, and the generation of monoclonal antibodies or other soluble factors which can alter biological activity of the β_2 integrins will provide practical means for therapeutic intervention in β_2 integrin-related immune and inflammatory responses."

This paragraph suggests that any member of the family may be useful in modulating inflammatory responses and makes no specific reference to α_d.

The Examiner also points to Gallatin, column 5, paragraph 5, as evidence of inflammatory conditions associated with α_d. However, Applicants note that this paragraph indicates that, <u>if</u> α_d is found on macrophages, it may allow for development of therapeutics to several immune diseases, such as multiple sclerosis. The disclosure proceeds to describe cloning a polynucleotide encoding human α_d, but does not confirm its expression on isolated macrophage cells.

Nothing in the disclosure of Gallatin discloses that anti-α_d antibodies bind to α_d on macrophages nor suggests that α_d antibodies would inhibit secretion of any cytokine associated with inflammation by macrophages.

Applicants submit that methods of treating an immune response does not require modulation of TNFα activity. Indeed, it is well-known in the art that inflammation can arise without involvement of TNFα at all. See e.g., Feliciani *et al.*, "A Th2-like cytokine response is involved in bullous pemphigoid. The role of IL-4 and IL-5 in the pathogenesis of the disease," *Int J Immunopathol Pharmacol.* 12:55-61. 1999 (Exhibit A), which teaches that the cytokines IL-4 and IL-5 promote inflammation in bullous pemphigoid, but TNFα is undetectable during such inflammation; and, Takashi *et al.*, "Spontaneous B-cell IgE production in a patient with remarkable eosinophilia and hyper IgE" *Ann Allergy Asthma Immunol.* 85:150-5, 2000 (Exhibit B), which discloses that eosinophilia may be induced by spontaneous production of IgE by B cells without stimulation by inflammatory cytokines, such as TNFα.

In addition, there is nothing in the later art, aside from the inventor's own work, that suggests that anti-α_d antibody modulates TNFα secretion. See Shanley *et al.*, "Requirements for α_d in IgG Immune Complex-Induced Lung Injury," *J. Immunol.* 160: 10-14-20, 1998 (Exhibit C), which indicates that α_d may be involved in lung inflammation, but this reference makes no mention of effects of α_d in spleen cells.

A worker of ordinary skill in the art might predict from the disclosure of Gallatin that a monoclonal antibody that blocks α_d binding to a receptor might modulate the inflammatory response by inhibiting accumulation or migration of cell types expressing α_d (e.g. leukocytes) to the site of inflammation. The blockade of ligand binding by an antibody is an extracellular event that a worker of skill might expect to take place given the specificity of an antibody. The present invention, however, is directed to the regulation of an intracellular event, TNFα expression, which one of ordinary skill would not necessarily expect when using an antibody to block binding to an extracellular molecule. For instance, Example 41, pages 151-152 of the specification shows that administering anti-α_d monoclonal antibody to an isolated population of cells (splenic phagocytes) decreases TNFα expression. This suggests that there is an intracellular response to specific to α_d monoclonal antibody binding that is not suggested in or predicted by reading Gallatin. The modulation of cell migration to a site of inflammation by α_d antibodies and the modulation of intracellular events are two different principles of inflammatory regulation by α_d antibodies that would not be reasonably expected by one of ordinary skill in the art.

Thus, Applicants submit that the rejection of claims 11, 12 and 14 under 35 U.S.C. § 102(b) should properly be withdrawn.

V. Conclusion

In view of the amendments and remarks made herein, Applicants submit that claims 11, 12 and 14 are in condition for allowance and respectfully request expedited notification of the same.

In conjunction with submission of this paper, Applicant submits herewith a Request for Continued Examination and a check in the amount of $770 pursuant to 37 CFR 1.17 (e). In the event any additional fees are due, the Assistant Commissioner is hereby authorized to deduct any additional fees from Marshall, Gerstein and Borun, LLP account number 13-2855.

Respectfully submitted,

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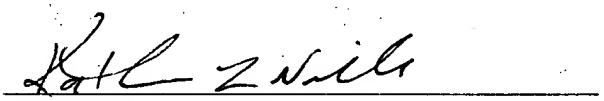
By: 

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